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(54) **TRICLOSAN AND SILVER COMPOUND CONTAINING MEDICAL DEVICES**

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(57) **ABSTRACT**

The present invention relates to polymeric medical articles comprising combinations of triclosan and silver-containing compounds. It is based, at least in part, on the discovery that these agents act synergistically, thereby permitting the use of relatively low levels of both agents. While it had been previously found that triclosan can be particularly useful when used in conjunction with chlorhexidine, it has been further discovered that medical articles having suitable antimicrobial properties may be prepared, according to the present invention, which contain triclosan without chlorhexidine. Such medical articles offer the advantage of preventing or inhibiting infection while avoiding undesirable adverse reactions to chlorhexidine by individuals that may have sensitivity to chlorhexidine.

20 Claims, No Drawings

no ODP

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THF and 30% v/v reagent alcohol and concentrations of 3% w/v 93A polyurethane and 1% w/v 60D polyurethane, having final concentrations of agents set forth in Table 20. Then segments were placed on petri dishes seeded with *Pseudomonas aeruginosa*. Table 3 illustrates the zones of inhibition of *Pseudomonas aeruginosa* over a three day period of Ag_2CO_3 and Ag_2CO_3 in combination with three phenolic compositions, (1) parachlorometaxylenol (PCMX), (2) o-phenyl phenol and (3) p-tertiary amyl phenol, and compared their respective efficacy to triclosan and Ag_2CO_3. As shown in Table 20 it appears that a synergistic effect occurs when chlorinated phenols are combined with silver salt exhibiting prolonged anti-microbial activity.

TABLE 20

	Zones of Inhibition (mm) DAY		
Drugs in Catheter	1	2	3
6% triclosan + 0.6% Ag_2CO_3	11	10	6
6% PCMX + 0.6% Ag_2CO_3	12	10	7
6% O-phenyl phenol + 0.6% Ag_2CO_3	10	0	0
6% p-tertiary amyl phenol + 0.6% Ag_2CO_3	10	0	0
0.6% Ag_2CO_3	10	0	0

19.0 ANTIMICROBIAL EFFICACY OF HYDROPHILIC OR HYDROPHOBIC MATRIX SYSTEMS BY ADDITION OF HYDROGEL POLYMER

We tested the effect on antimicrobial activity of adding a hydrogel polymer such as polyvinyl pyrrolidone (PVP) to treatment solutions containing triclosan, silver compound, and polyurethanes, and then using such solutions to treat medical devices. Polyurethane catheter segments were dipped in one of the following two treatment solutions:

(i) a treatment solution prepared by mixing 30% v/v reagent alcohol (containing triclosan and silver carbonate) with 70% v/v THF (containing 93A and 60D polyurethanes), having final concentrations of 6% w/v triclosan, 0.4% w/v silver carbonate, 3% w/v 93A polyurethane, and 1% w/v 60D polyurethane; or

(ii) a treatment solution prepared by mixing 30% v/v reagent alcohol (containing triclosan and silver carbonate) with 70% v/v THF (containing 60D polyurethane and PVP), having final concentrations of 6% w/v triclosan, 0.4% w/v silver carbonate, 3% w/v 60D polyurethane, and 2% w/v PVP.

The treated catheter segments were then dried for 24 hours and then tested for antimicrobial activity by measuring the zones of inhibition The antimicrobial properties of the material were then tested by measuring the zones of inhibition produced against *S. epidermidis* and *P. aeruginosa* after placing the treated material on a trypticase soy agar plate seeded with 0.3 ml of 10^8 cfu/ml bacterial culture and incubating at 37° C. for 24 hours. In addition, the amount of triclosan present per centimeter of catheter was determined spectrophotometrically. The results are shown in Table 21.

TABLE 21

Compounds in Treatment Solution	Zones of Inhibition (mm) μg TC/cm	vs. *S. epidermidis*	vs. *P. aeruginosa*
6% TC + 0.4% Ag_2CO_3 + 3% 93A PU + 1% 60D PU	425	11	6.5
6% TC + 0.4% Ag_2CO_3 + 3% 60D PU + 2% PVP	397	18	10

In other experiments, the effect of PVP incorporated into a hydrophobic article, i.e., Dacron material for LVAD drive lines, was determined. In particular, pieces of Dacron were uniformly spread with one of the two following treatment solutions:

(iii) a treatment solution prepared by mixing 10% v/v reagent alcohol (containing triclosan, chlorhexidine diacetate (CHA), chlorhexidine free base (CHX) and silver sulfadiazine) with 90% v/v THF (containing 93A and 60D polyurethanes), having final concentrations of 0.2% w/v triclosan, 0.3% w/v chlorhexidine diacetate, 0.2% w/v chlorhexidine free base, 0.2% w/v silver sulfadiazine, 4% w/v 93A polyurethane, and 1% w/v 60D polyurethane, or

(iv) a treatment solution prepared by mixing 10% v/v reagent alcohol (containing triclosan, chlorhexidine diacetate (CHA), chlorhexidine free base (CHX) and silver sulfadiazine) with 90% v/v THF (containing 93A and 60D polyurethanes and PVP and polyvinylchloride ("PVC")), having final concentrations of 0.2% w/v triclosan, 0.3% w/v chlorhexidine diacetate, 0.2% w/v chlorhexidine free base, 0.2% w/v silver sulfadiazine, 4% w/v 93A polyurethane, 1% w/v 60D polyurethane, 2% w/v PVP and 4% w/v PVC.

The treated Dacron was allowed to dry for 24 hours and then attached to the outer surface of silicon tubing using a silicon adhesive to produce a drive line. The resulting drive lines were then tested for antimicrobial activity by measuring the zones of inhibition produced against *S. epidermidis*, *P. aeruginosa*, and *C. albicans* after placing the treated material on a trypticase soy agar plate seeded with 0.3 ml of 10^8 cfu/ml bacterial or yeast culture and incubating at 37° C. for 24 hours. In addition, the amounts of triclosan and chlorhexidine present per centimeter of Dacron were determined spectrophotometrically. The results are shown in Table 22.

TABLE 22

Group	μg TC/cm	μg CHX/cm	Zones of Inhibition (mm) v. *S. epidermidis*	v. *P. aeruginosa*	v. *C. albicans*
LXI	387	662	17	11.5	14
LXII	420	480	22	15	16

As illustrated in Tables 21 and 22, the use of a hydrogel such as PVP in a hydrophilic (e.g., polyurethane) or hydrophobic (e.g., PVC) matrix allows better drug release as evidence by greater zones of inhibition.

Various publications are cited herein, which are hereby incorporated by reference in their entireties.

We claim:

1. An anti-infective medical article prepared by exposing a polymer-containing medical article, for an effective period of time, to a treatment solution comprising between about

0.3 and 1.5 percent of a silver salt and between about 0.1 and 20 percent triclosan, where the treatment solution and the medical article do not contain chlorhexidinie or a chlorhexidine salt.

2. The anti-infective medical article of claim 1, where the treatment solution further comprises an organic acid at a concentration of between about 0.1 and 5 percent.

3. The anti-infective medical article of claim 2, where the organic acid is citric acid.

4. The anti-infective medical article of claim 1, where the treatment solution further comprises an anti-inflammatory agent, at a concentration of between about 1 and 5 percent.

5. The anti-infective medical article of claim 4, where the anti-inflammatory agent is salicylic acid or a derivative thereof.

6. The anti-infective medical article of claim 1, where the treatment solution further comprises an additional antimicrobial agent.

7. The anti-infective medical article of claim 6, where the additional antimicrobial agent is selected from the group consisting of gramicidin, polymixin, norfloxacin, sulfamylon, polyhexamethylene biguanide, alexidine, minocycline, iodine, benzalkonium chloride and rifampicin.

8. The anti-infective medical article of claim 1, where the treatment solution further comprises between about 1 and 5 percent of one or more hydrophilic or hydrophobic polymer.

9. The anti-infective medical article of claim 1 which is a polytetrafluoroethylene patch.

10. A polymer-containing vascular catheter comprising between about 100 and 600 micrograms of triclosan in releasable form per centimeter and between about 25 and 100 micrograms of silver atom or ion in releasable form per centimeter, where the catheter does not contain chliorhexidine or a chlorhexidine salt.

11. A method of preparing an anti-infective medical article comprising exposing a polymer-containing medical article, for an effective period of time, to a treatment solution comprising between about 0.3 and 1.5 percent of a silver salt and between about 0.1 and 20 percent triclosan, where the treatment solution and the medical article do not contain chlorhexidine or a chlorhexidine salt.

12. The method of claim 11, where the treatment solution further comprises an organic acid at a concentration of between about 0.1 and 5 percent.

13. The method of claim 12, where the organic acid is citric acid.

14. The method of claim 11, where the treatment solution further comprises an anti-inflammatory agent, at a concentration of between about 1 and 5 percent.

15. The method of claim 14, where the anti-inflammatory agent is salicylic acid or a derivative thereof.

16. The method of claim 11, where the treatment solution further comprises an additional antimicrobial agent.

17. The method of claim 14, where the additional antimicrobial agent is selected from the group consisting of gramiciain, polymixin, norfloxacin, sulfamylon, polyhexamethylene biguanide, alexidine, minocycline, iodine, benzalkonium chloride and rifampicin.

18. The method of claim 11, where the treatment solution further comprises between about 1 and 5 percent of one or more hydrophilic or hydrophobic polymer.

19. The method of claim 11, where the polymer-containing medical article is a polytetrafluoroethylene patch.

20. An anti-infective medical article prepared by exposing a polymer-containing medical article, for an effective period of time, to a treatment solution comprising between about 0.3 and 1.5 percent of a silver salt and between about 0.1 and 20 percent triclosan, where the treatment solution and the medical article do not contain chlorhexidine or a chlorhexidine salt, and where the article comprises polytetrafluoroethylene polymer.

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